1. Introduction

One of the chronic complications of the Type II Diabetes, the Diabetic peripheral neuropathy (DPN) affecting almost 50% of patients.[1, 2] Diabetic neuropathy was defined "after the exclusion of other causes as the peripheral nerve dysfunction with existence of symptoms and/or signs in diabetic individuals" by the members of the International Consensus Meeting.[3]

Chronic sensory and motor diabetic peripheral neuropathy (CSMDPN) is commonest symmetrical type; with an insidious or gradual onset and the prevalence of it increases with the age, longer diabetes duration, in male population, higher percentage of glycosylated haemoglobin (HbA1C); in smokers, peripheral vascular problem and insulin users.[4,5] Individuals with CSMDPN are seen with neuropathic pain and altered neural mechanosensitivity, balance and gait problems[6,7] due to impaired proprioception,[8] limited ankle joint movement and reduced muscle flexibility.[9,10]

Early detection of lesions and the treatment in the DPN can prevent the end stage complications. The late detection, progression and treatment of it yields in the deterioration of the quality of life of the sufferers and also increase the risk of foot and lower limb amputations.[11] There are many tools to detect the peripheral neuropathy like NCS, ultrasonography, and MRI.[12] Nerve conduction studies (NCS) and the clinical assessment is the basis for the DPN diagnosis.[13] NCS parameters in the form of motor and sensory nerve conduction velocities were found decreased in these patients.[14]

Recent sensitive detection tool; the Diffusion Tensor Imaging (DTI) may be used in the finding of peripheral nerve related disease and also monitor reinnervation through fractional anisotropy (FA), apparent diffusion coefficient (ADC). Physiologically, in intact peripheral nerves the preference of direction indicated by FA has high value of free water proton diffusion. FA maps are sufficient marker in the detection of focal peripheral neuropathy in very early or subclinical stages of it; NCS are unable to detect these changes. FA values are reduced in the presence of extracellular fluid accumulation and in the presence of wide extracellular space resulted because of less number of fibers. ADC values, under the movement restriction reflect the diffusivity of the molecules and are increased in the presence of demyelination and fluid

accumulation. Both the DTI parameters are significantly dependent on the intact myelin sheath in the nerve fibers.[15]

Hyperglycemia leads to the fluid accumulation in the nerve causing the axonal injury and the demyelination, further leading to the altered nerve biomechanics.[16] The altered mechanosensitivity of the nerve in the DPN can be targeted through nerve mobilization (NM) in the form of the neurodynamics (sliders and tensioners) and the nerve massage.[17, 18] It is safe to perform the lower extremity neurodynamics in the patients with diabetes mellitus.[19] The NM has shown the improvement in the nerve conduction studies parameters in the peripheral neuropathy patients with and without the conservative non neural interventions. The NM techniques are useful in restoring the normal physiological function through both the intraneural and extra neural effects.[20, 21]

The influence of NM on the Magnetic Resonance Neurography (MRN) method with DTI has not been explored yet. Thus, the purpose of current research is to explore the effect of NM on the DTI parameters in DPN patients.

1.1 Statement of the Problem:

DPN induced peripheral neuropathic pain in the lower extremities results through the ischemia, accumulation of extracellular and intraneural edema, and the inflammation of the nerve, and thus leads to impaired nerve movement in the nerve bed or its mechanical interface. This reduced nerve mobility can be addressed through neural manual therapy. The pathophysiological neural changes have an impact on the DTI parameters. To the best of our knowledge literature on the influence of NM on the DTI parameters could not be found.

1.2 Purpose of the study:

To investigate and explore the NM intervention on DTI parameters in DPN patients.

1.3 Study Objectives:

1.3.1 To measure the DTI values in matched asymptomatic controls and in patients with DPN.

1.3.2 To evaluate the efficacy of NM along with conventional treatment on DTI parameters in patients with DPN.

1.3.3 To evaluate the efficacy of Conventional treatment on DTI parameters in patients with DPN.

1.3.4 To compare the efficacy of NM and Conventional treatment on DTI parameters in patients with DPN.

1.4 Research Hypothesis:

1.4.1 **Null Hypothesis:**

a) There will be no significant effect of NM along with Conventional treatment on the DTI values in tibial nerve in patients with DPN.

b) There will be no significant effect of Conventional treatment on the DTI values in tibial nerve in patients with DPN.

1.4.2 **Alternate Hypothesis:**

a) There will be significant effect of NM along with Conventional treatment on the DTI values in tibial nerve in patients with DPN.

b) There will be significant effect of Conventional treatment on the DTI values in tibial nerve in patients with DPN.

2. REVIEW OF LITERATURE:

3. METHODOLOGY:

3.1 Study Design

Multigroup pretest-posttest design will be used.

3.2 Ethical Clearance

The research proposal will be submitted to the Institutional Research Ethics Committee of Maharishi Markandeshwar (Deemed to be University), Mullana- Ambala, and Haryana, India.

3.3 Study Setting

3.3.1 Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation outpatient department.

3.3.2 Maharishi Markandeshwar Institute of Medical Sciences and Research- Radiology Outpatient department

3.4 Sampling

Purposive sampling (Criterion - based) will be used.

3.5 Criteria for selection of Participants:

3.5.1 Inclusion criteria:

3.5.1.1 Individuals with confirmed chronic sensory motor diabetic peripheral neuropathy (CSMDPN) diagnosed by physician as per diagnostic criteria.[22]

3.5.1.2 Individuals with unilateral or bilateral CSMDPN.

3.5.1.3 Aged between 36 – 70 years.

3.5.1.4 Both female and male.

3.5.1.5 Individuals who will give the informed consent.

3.5.1.6 Individuals with Type 2 diabetes, with HbA1C <10%.

3.5.2 Exclusion criteria:

3.5.2.1 History of cardiac pacemakers and MRI contraindications.

3.5.2.2 Diabetic foot ulcer and Neuropathic joints.

3.5.2.3 Any deformity induced due to musculoskeletal or neurological involvement.

3.5.2.4 Central nervous system and autonomic nervous system pathology.

3.5.2.5 Any other co morbidities.

3.6 Sample Size:

The sample size based on selection criteria will be 90 patients.

3.7 Study Variables

3.7.1 Independent variables

3.7.1.1 NM

3.7.1.2 Conventional treatment

3.7.2 Dependent variables

3.7.2.1 Conceptual:

3.7.2.1.1 DTI parameters: FA and ADC

3.7.2.1.2 Pain

3.7.2.1.3 Disability

3.7.2.2 Operational:

3.7.2.2.1 MRI 1.5- Tesla MR System Multiva- Philips magnet, Baltimore, Netherland, Holland

3.7.2.2.2 Visual Analog Scale

3.7.2.2.3 Neuropathy specific quality of life questionnaire (Appendix - B)

The Visual Analog Scale (VAS) is the pain measurement scale which is most commonly used with high reliability (ICC = 0.98). It is a 100 mm horizontal or vertical straight line with description of no pain at one end and worst pain on the other end of the line respectively. The patients will be instructed to report the intensity of pain experienced at that moment with a mark on the line. Pain measurement scoring is done in the millimeters from the no pain end of the scale to the mark by the patient on line.[23]

Neuropathy specific quality of life questionnaire (Neuro QoL) is used in the diabetic peripheral neuropathy patient's assessment and follows up after treatment intervention. It assesses the physical and emotional aspects related to quality of life and daily living of the diabetic neuropathy patients. Neuro QoL questionnaire is divided into six sub scales with total 27 questions having 5 – point Likert scale for each question, where 1 represents "never" and 5 represents "all the time" frequency of symptoms. Six sub scale domains includes, pain and parasthesias; loss of temperature and object feeling in the feet; impaired standing and walking balance; restriction in activities of daily living; interpersonal physical and emotional dependence; emotional distress and two additional questions to assess the overall influence of neuropathy on life quality.[24]

3.8 Outcome Measures

3.8.1 Primary Outcome Measure

3.8.1.1 DTI parameters – FA & ADC

3.8.2 Secondary Outcome Measure

3.8.2.1 Pain

3.8.2.2 Disability

3.9 Procedure:

The selection of the 90 patients will be done using the criteria – based purposive sampling. Random allocation of the eligible subjects for treatment will be done by the sealed opaque envelope method. All the subjects will sign the informed consent (Appendix - A) for participation in the study. Subjects will be randomized using the computer generated randomization method into three groups: Group A (NM+ Conventional treatment) and Group B (Conventional treatment alone) and Group C (Sham intervention). In healthy matched control group, age and sex matched non diabetic subjects with no symptoms of neuropathy will be included.

The baseline data for FA and ADC, pain and disability will be recorded using the MRI 1.5- Tesla MR System Multiva- Philips; VAS and universal goniometer respectively. During the treatment period patients will follow their medical treatment protocol without any alteration in their medical management; if there is any alteration then the patient will be excluded from further analysis and there data will be considered for analysis using intention to treat analysis method. **(Figure. 1)**

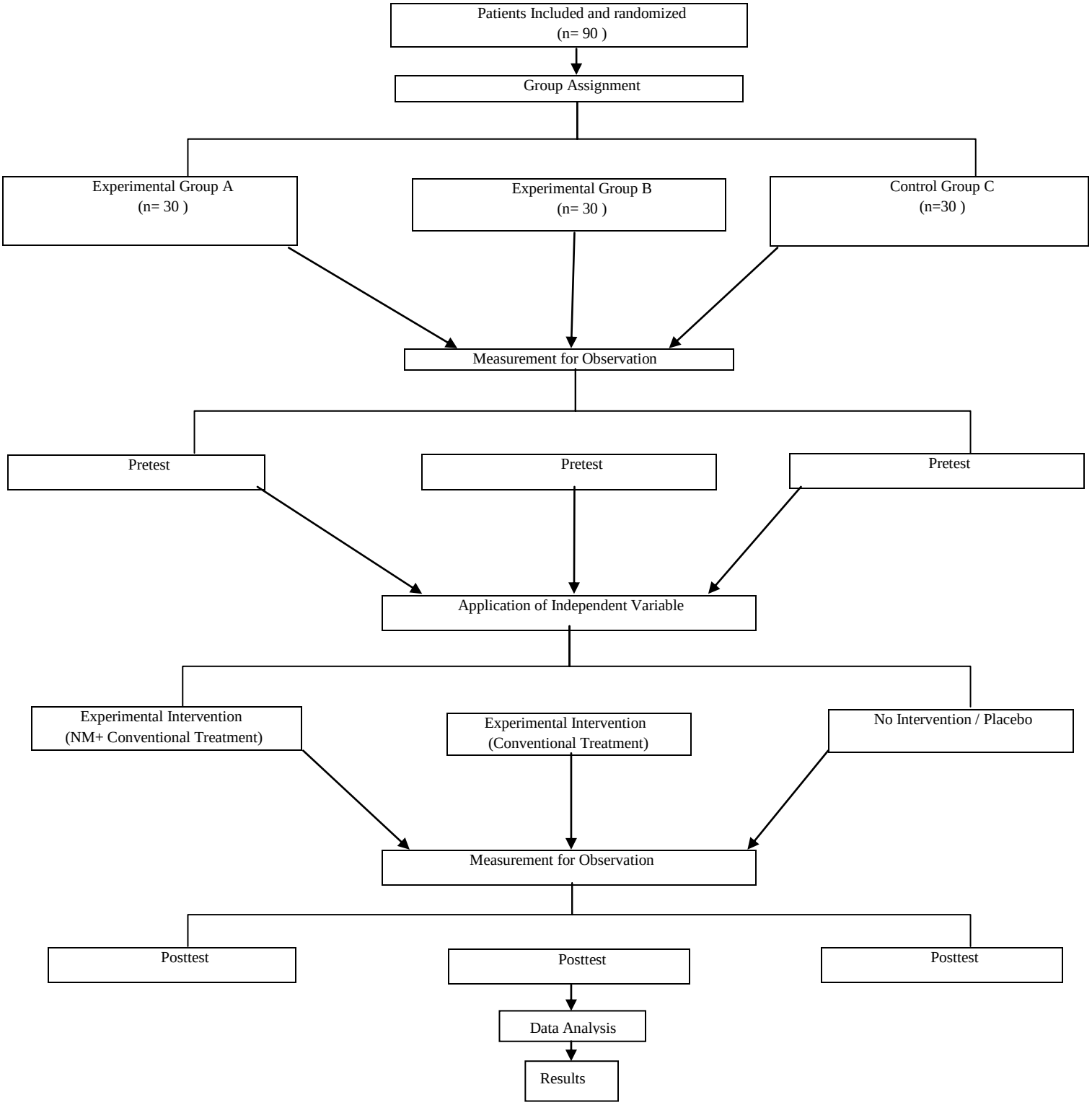

Figure.1 – Flow chart to show the protocol

Investigation:

MRI technique will be performed by the experienced radiologist having more 10 years or more of experience using the 1.5- Tesla MR System Multiva- Philips magnet, Baltimore, Netherland, Holland with a typical spine/knee range loop with the magnetic field centered on the ankle joint. MRI scans of the conventional leg will also be done. "The conventional MRI sequences will include axial and sagittal T2WSE and STIR for pathoanatomic relationship. The imaging parameters for T2WSE will be TR = 2513 – 2932ms, TE = 90ms, NEX = 3, FOV = 15 -33 cm, Matrix size = 256 x 256, voxel size = 0.99\1.26\3.66 mm, slice thickness/gap = 1.5 – 4mm\0.1 – 0.8mm) and for STIR will be TR = 5000ms, TE = 70ms, TI = 160ms, flip angle = 90 NEX = 4, Matrix size = 256 x 192, voxel size = 1.42\2.06\13mm, slice thickness\gap = 1.5 – 4mm\ 0.1 – 0.8mm respectively. Axial T1WSE images for baseline anatomic and isotropic restoration will be acquired with the parameter TR = 577, TE = 8, NEX = 3, FOV = 20 – 33 cm, voxel size = 0.99\1.22\3.66 mm, slice thickness\gap = 1.5 – 4mm\0.1 – 0.8mm." [25] Free – breathing single – shot echo – planar Diffusion weighted images (DWI) neurography will be done by means of couple of b – values of 0 and 800 s/mm^2 respectively. [26] ADC and FA data will be procured by adding the axial DWI and axial DTI sequences respectively.

Intervention:

Nerve Mobilization Technique [27] –

- Proximal Sliding of the tibial nerve:

  Patient Position – will be supine lying.

  Therapist Position – will be standing by the side of the patient couch.

The therapist will hold the patient lower extremity in the horizontal position with the hip at 45 degree of flexion. The movement components to mobilize the nerve will be in a sequence of dorsiflexion (DF) and eversion (Ev) at the ankle and foot with DF of toes; knee extension and proper stabilization will be provided to the remaining lower extremity joints. At the end of the nerve bias, DF of the foot and toes will be released in the plantarflexion movement to allow the tibial nerve to slide proximally further.

- Distal Sliding of the tibial nerve:

  Patient Position – will be supine lying.

  Therapist Position – will be standing by the side of the patient couch.

The therapist will hold the patient lower extremity in the horizontal position with the hip at 45 degree of flexion. The nerve will be moved into its mechanical interface distally by adding DF and Ev of the foot and also adding the DF of toes for releasing the proximal tension and allow the nerve to slide distally.

- Tensioner technique of the tibial nerve:

  Patient Position – will be supine lying.

  Therapist Position – will be standing by the side of the patient couch.

  Movement Components – Hip flexion 45 degrees with ankle DF and foot Ev with extension at knee joint.

  The NM will be done by the experienced physiotherapist for 2 times/ week for 3 weeks and the patients will receive 5 sets of 10 cycles with a rest period of 1 minute in each set. [28]

Nerve Massage [29] –

Both the longitudinal and transverse nerve massage will be done by the experienced physiotherapist for 2 times/ week for 3 weeks along the course of the tibial nerve (popliteal fossa to foot) for 4 minutes in total and the patients will receive total of 6 times for 10 repetitions.

Transcutaneous Electrical Nerve Stimulation (TENS) [30] –

Patients will receive 10 sessions of TENS (80 Hz, 50 Amp, 0.2 ms square pulses, 2 to 3 times sensory threshold) every alternate day for 3 weeks for 20 minutes, with one electrode placement over the proximal tibia and other electrode over the ankle.

DATA ANALYSIS

The Normality test, Kolmnogorov Smirnov will be used to check the normal distribution of the sample size. Appropriate statistical test will be used to achieve the aims of study like Mean, standard deviation (SD) and the level of significance (LOS) will be kept at 0.05 with 95% confidence interval (CI). Within the group analysis will be performed using repeated measures ANOVA if normal, otherwise Friedman test if not normal and between the group analysis will be done by independent t – test if normal, or Mann U Whitney if not normal.